the growth of lymphatic endothelial cells a composition comprising said polypeptide, in an amount effective to modulate the growth of lymphatic endothelial cells in vivo.

40. (New) A method according to claim 19, further comprising a step of purifying the secreted polypeptide prior to the contacting step.

REMARKS

I. Status of Claims

Claims 1-5, 7-9, 11-37, and 40 are pending in the instant application. Attached for the Examiner's convenience is a marked-up version of the amendments to the specification (Appendix A), a marked-up version of the amended claims (Appendix B), and a complete set of pending claims (Appendix C). This amendment includes no new matter.

Claims 5, 19, 28, 31, 33, and 37-39 were amended or canceled to remove nonelected and withdrawn subject matter. These amendments were made to comply (in part) with the Examiner's restriction requirement, and not for any reasons relating to patentability. The resulting amendment to claim 5 introduced limitations from claims 6 and 10, making it possible to delete these claims as well. The Applicants reserve the right to pursue the nonelected subject matter in related applications, such as divisional applications.

Claim 40 was introduced to adopt a suggestion made by the Examiner in the Office action.

II. The priority claim of the instant application has been updated.

In paragraph 5 of the office action, the Examiner noted that the instant application lacked the current status of some of the parent applications. In response, the Applicants have amended the specification to provide the current status of the parent applications.

The Applicants also have dropped their 1994 priority claim, solely to extend the duration of the eventual patent.

III. The Applicants request consideration of WO 98/49300.

The Examiner indicated that reference B17 in the IDS (WO 98/49300) was not considered because the Applicants mistakenly sent a different document. The correct document is included herewith, and consideration thereof is requested.

IV. The objections to claim 5 for informalities and claims 1, 5, 6, 11, 12, 19 and 20 for encompassing a non-elected invention should be withdrawn.

In paragraphs 6.1-6.2, the Examiner objected to claims 1, 5, 6, 11, 12, 19, and 20 for allegedly "encompassing a non-elected invention. The claims should be amended to recite the elected invention or deleted."

Solely for the purposes of this application, the Applicants will concede that methods of regulating endothelial cell growth or treating a patient with agonist VEGF-C polypeptide materials is a distinct invention from methods that involving using an antibody to VEGF-C or other antagonist materials. Accordingly, the latter subject matter has been removed from claims by way of amendment, solely because it is subject matter drawn to a non-elected invention. The Applicants reserve the right to pursue such subject matter in related applications.

The Applicants also have canceled nonelected claims 38-39.

The Applicants continue to traverse the other bases for restriction and reserve the right to petition therefrom. The Patent Office's admission that "the different subgroups comprises a minimum recited portion of SEQ ID NO: 8, and also comprises successively larger VEGF-C polypeptide fragments that include the minimum recited portion" is incompatible with maintaining the restriction requirement. The Patent Office has failed to support its allegation of "different activities, properties and effects" with respect to the amended claim set, from which "antagonistic effects" have been withdrawn by

amendment. While it may be true that the different subgroups possess some different properties, they also share common properties attributable to their common VEGF-C sequence, such as VEGFR-3-activating properties. The Applicants are presently claiming methods of use, and the common properties support rejoinder with respect to the particular methods claimed.

The Patent Office is reminded that, when an application contains claims linking distinct inventions, proper procedure is to examine the entirety of the claims, not to request deletion of non-elected subject matter at the outset. As explained in the MPEP, "The linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn. Any claim(s) direct to the nonelected invention(s), previously withdrawn from consideration, which depends from or includes all the limitations of the allowable linking claim must be rejoined and will be fully examined." (MPEP 809.) The MPEP even explains that applicants should be given the opportunity to reintroduce any canceled, nonelected claims which meet these qualifications but which were canceled in response to a restriction.

Accordingly, the Applicants request reconsideration in view of the MPEP's procedure for handling generic and/or linking claims, and believe that either petitioning from the restriction or deleting "nonelected" subject matter from claims is premature at this time.

V. The objection to the specification for failing to provide antecedent basis for the claimed subject matter should be withdrawn.

In paragraph 6.3 of the office action, the Examiner alleged that claim 19 recites hybridization conditions that are not taught (elsewhere) in the specification. In fact, the hybridization conditions described in Example 10 at page 43, lines 8-12, are the same hybridization conditions as recited in claim 19. All of the parameters for hybridization recited in claim 19 (time, temperature, solutions, etc.) are clearly set out in Example 10 of the specification. Accordingly, the objection to the specification should be withdrawn.

VI. The rejection of claims 1, 3-8, 11-14, 19, 20 and 23-26 under 35 U.S.C. 112, first paragraph, should be withdrawn.

In paragraph 7.1 of the Office action, the Examiner rejected claims 1, 3-8, 11-14, 19, 20 and 23-26 under 35 U.S.C. 112, first paragraph, because the Examiner believes that the specification, while being enabling for stimulating endothelial cell growth, does not reasonably provide enablement for regulating or modulating endothelial cell growth. The Applicants dispute this characterization of the application. However, in view of the restriction requirement and the elected subject matter, the basis for rejection is moot, and should be withdrawn. Most of the claims were amended to include recitations relating to "stimulating" in view of the restriction requirement.

Claim 1 of the application is indeed directed to a method of "regulating" endothelial cell growth. However, the claim recites using a polypeptide that "binds the extracellular domain of Flt4 receptor tyrosine kinase and stimulates Flt4 autophosphorylation." Thus, the claim is already commensurate in scope with subject matter that the Examiner concedes to be enabled.

At paragraph 7.2 of the office action the Examiner rejected claims 5-14 under 35 U.S.C. 112, first paragraph, alleging that the specification does not reasonably provide enablement for a method of treatment of a patient by identifying a patient in need of modulation of Flt4 activity. In the rejection, the Examiner acknowledges that the application IS enabling "for stimulation of endothelial cell growth by activation of Flt4 receptor in vitro or in vivo with the small fragment of VEGF-C . . . ." Clarification is in order.

Claim 5 is written as a two step claim. Importantly, the second step of the claim is directed to "administering to the patient a composition comprising a purified polypeptide in an amount effective to modulate the activity of Flt4, wherein the polypeptide binds the extracellular domain (EC) of Flt4 and stimulates Flt4 phosphorylation in mammalian cells expressing Flt4, said polypeptide comprising an amino acid sequence comprising a portion of SEQ ID NO: 8 effective to permit such binding." Thus, claim 5 involves using a VEGF-C polypeptide to stimulate Flt4 -- precisely the type of subject matter that the Examiner concedes to be enabled.

The first step of the claim is not the treatment step per se, but rather a step of selecting whom to treat. In other words, the step of "identifying a patient in need of modulation of Flt4 activity" should not be read in isolation as the treatment per se, but rather, should be read as the identification of whom should receive the VEGF-C treatment.

Because the claim is directed to subject matter that the Examiner concedes to be enabled, the rejection should be withdrawn.

VII. The rejection of claims 19, 20 and 23-26 under 35 U.S.C. 112, second paragraph, should be withdrawn.

In paragraph 8 of the office action, the Examiner rejected claim 19, 20 and 23-26 under under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that claim 19 is indefinite because it is drawn to a method that is missing a purification step, thereby making it an incomplete method. The Applicants respectfully traverse.

While it is true that claim 19 does not recite a purification step, it is equally true that the method can be practiced without a purification step. For example, in the context of treatment of a patient, one skilled in the art could transform a cell from the patient, and then reintroduce the cells into the patient to express and secrete the Flt4 ligand, which would then contact Flt4-expressing cells in the patient. Likewise, the method can be practiced on Flt4-expressing cells that have themselves been isolated (e.g., for ex vivo expansion). Isolated Flt4-expressing cells could be contacted with conditioned media from the transfected cells which contains the secreted polypeptide -- purification would not be critical. Thus, while purification of the Flt4 ligand may be desirable or preferable in some contexts, it is not necessary for practicing every embodiment of the invention. Therefore, the claim as written in not incomplete - it simply embraces embodiments with purifications and embodiments without.

For these reasons, the rejection for indefiniteness should be withdrawn.

VIII. Conclusion.

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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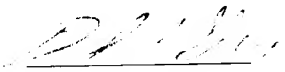
By: 

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APPENDIX A

MARKED-UP VERSION OF AMENDMENTS TO THE SPECIFICATION

At page 1, lines 3-15:

This application is a continuation of U.S. Patent Application No. 09/355,700, which is a 35 USC §371 U.S. National Stage filing of International Application No. PCT/US98/01973, filed February 2, 1998, **now U.S. Patent No. 6,361,946 which** [This application also] is a continuation-in-part of United States Patent Application Serial No. 08/795,430, filed February 5, 1997, **now U.S. Patent No. 6,130,071**. This patent application also is a continuation-in-part of International Patent Application PCT/FI96/00427, filed August 01, 1996; and a continuation-in-part of United States Patent Application Serial No. 08/671,573, filed June 28, 1996; and a continuation-in-part of United States Patent Application Serial Number 08/601,132, filed February 14, 1996, **now U.S. Patent No. 6,403,088**; and a continuation-in-part of United States Patent Application Serial Number 08/585,895, filed January 12, 1996, **now U.S. Patent No. 6,245,530**; and a continuation-in-part of United States Patent Application Serial Number 08/510,133, filed August 1, 1995, **now U.S. Patent No. 6,221,839** [and a continuation-in-part of United States Patent Application Serial Number 08/340,011, filed November 14, 1994, now U.S. Patent No. 5,776,755].

APPENDIX B

MARKED-UP VERSION OF AMENDMENTS TO THE CLAIMS

5. (Amended) A method of modulating the activity of Flt4 receptor tyrosine kinase (Flt4), comprising the steps of:

identifying a patient in need of modulation of Flt4 activity; and

administering to the patient a composition comprising a purified polypeptide in an amount effective to modulate the activity of Flt4, wherein the polypeptide [is selected from the group consisting of:

(a) a polypeptide that] binds the extracellular domain (EC) of Flt4 **and stimulates Flt4 phosphorylation in mammalian cells expressing Flt4**, said polypeptide comprising an amino acid sequence comprising a portion of SEQ ID NO: 8 effective to permit such binding[; and

(b) an antibody which is specifically reactive with the polypeptide of (a)].

19. (Amended) A method of modulating the activity of Flt4 receptor tyrosine kinase (Flt4) in Flt4-expressing cells, comprising the steps of:

(a) preparing a polynucleotide comprising a nucleotide sequence that encodes a polypeptide that binds to the extracellular domain of human Flt4,

wherein said polynucleotide includes a strand that hybridizes to a DNA comprising the non-coding strand complementary to SEQ ID NO: 32, under the following hybridization conditions:

(i) hybridization at 42°C for 20 hours in a solution containing 50% formamide, 5x SSPE, 5x Denhardt's solution, 0.1% SDS and 0.1 mg/ml denatured salmon sperm DNA; and

(ii) washing the filter twice for thirty minutes at room temperature and twice for thirty minutes at 65°C with a wash solution containing 1x SSC, and 0.1% SDS;

(b) transforming or transfecting a cell with the polynucleotide such that the cell expresses and secretes a polypeptide encoded by said polynucleotide, wherein said secreted polypeptide binds the extracellular domain of human Flt4**, stimulates Flt4 autophosphorylation,** and has a molecular weight of about 23 kD as assessed by SDS-PAGE under reducing conditions; and

(c) contacting Flt4-expressing cells with the secreted 23 kD polypeptide.

28. (Amended) A method of [modulating] **stimulating** the proliferation of mammalian endothelial cells comprising the step of contacting mammalian endothelial cells with a composition comprising a polypeptide in an amount effective to modulate the proliferation of mammalian endothelial cells, said polypeptide comprising a VEGF-C *C156 polypeptide that binds to human Flt4 receptor tyrosine kinase (Flt4) and fails to bind to human KDR receptor tyrosine (VEGFR-2), said polypeptide having an amino acid sequence comprising a portion of SEQ ID NO: 8 effective to permit binding to Flt4, wherein the cysteine residue at position 156 of SEQ ID NO: 8 has been deleted or replaced by another amino acid.

31. (Amended) An in vivo method according to claim 28, wherein the contacting step comprises administering to a mammalian subject in need of [modulation] **stimulation** of the growth of lymphatic endothelial cells a composition comprising said polypeptide, in an amount effective to [modulate] **stimulate** the growth of lymphatic endothelial cells in vivo.

33. (Amended). A method of [modulating] **stimulating** the proliferation of mammalian endothelial cells comprising the step of contacting mammalian endothelial cells with a composition comprising a polypeptide in an amount effective to [modulate] **stimulate** the proliferation of mammalian endothelial cells, said polypeptide comprising a fragment of a vertebrate prepro-VEGF-amino acid sequence that binds to human Flt4 receptor tyrosine kinase, with the proviso that, in said polypeptide, a conserved cysteine of the vertebrate prepro-VEGF-C has been deleted or replaced by another amino acid,

wherein the vertebrate prepro-VEGF-C amino acid sequence comprises an amino acid sequence that is encoded by a DNA of vertebrate origin which hybridizes to a non-coding strand complementary to nucleotides 352 to 1611 of SEQ ID NO: 7 under the following hybridization conditions: hybridization at 42°C in a hybridization solution comprising 50% formamide, 5 X SSC, 20 mM Na•PO4, pH 6.8; and washing in 0.2 X SSC at 55°C,

wherein nucleotides 352 to 1611 of SEQ ID NO: 7 encode a human prepro-VEGF-C having the amino acid sequence set forth in SEQ ID NO: 8 that is characterized by eight cysteine residues at positions 131, 156, 162, 165, 166, 173, 209, and 211 of SEQ ID NO: 8 that are conserved in human vascular endothelial growth factor (VEGF), human platelet derived growth factors A and B (PDGF-A, PDGF-B), human placenta growth factor (PlGF-1), and human vascular endothelial growth factor B (VEGF- B), and

wherein the conserved cysteine that has been deleted or replaced corresponds to position 156 of SEQ ID NO: 8.

37. (Amended) An in vivo method according to claim 33, wherein the contacting step comprises administering to a mammalian subject in need of [modulation] **stimulation** of the growth of lymphatic endothelial cells a composition comprising said polypeptide, in an amount effective to modulate the growth of lymphatic endothelial cells in vivo.

40. (New) A method according to claim 19, further comprising a step of purifying the secreted polypeptide prior to the contacting step.